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When You Reach a Fork in The Road, Take It: Science and Product Development as Linked Paths

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I. INTRODUCTION

Increasingly, health is recognized as a major force for economic development; and because economic development is central to political and social stability, health is being looked at as the great hope for the future of the world, as population sizes and disparities among them increase. This perspective has been growing ever since the 1993 World Development Report was released by the World Bank, and it has fueled an intensive scrutiny of health care around the world, focusing on systems and health care delivery on the one hand, and equitable access to the products of research on the other hand. In the middle of all of is this is a concern about how health care (which must include both the training of personnel from the basic low level health care worker to the physician), and research and development (which must include the financing of research in academia and the development of products primarily in the private sector) are organized, and how they do or do not address inequities between and within populations and nations. The purpose of this paper is to provide a perspective from the vantage point of a physician researcher, and to make the case that inclusion of the education and career development pathways of health researchers within the ongoing discussions on the health care and research "system" is essential to achieving future outcomes that, at present, can only be dreamed of. In essence, the argument will be that the education and research system must ensure that the scientific workforce will understand public health needs, that the public health workforce will understand the contributions of science, and that the financial and organizational mechanisms that create the private good of products for better health care can address the global public good requirements for global development.

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II. PARADIGMS OF SCIENCE

The goals of science are to both create new knowledge and better understanding of old knowledge through a method that is objective and self-validating through constant re-exploration of principles seen to be "established" in order to sustain or refute that judgment. The scientific method is based on gathering observable, empirical, and measurable evidence subject to specific principles of reasoning. In other words, this method is the collection of data through observation and experimentation, and the formulation and testing of hypotheses. As I grew up as a physician-scientist, the system in which we operated within academia was one that rewarded scientific discovery and accomplishment for itself. Our career paths were crudely defined as "publish or perish," the never ending cycle in which research grants support research, papers are published, follow-on research grants are prepared, and academic advancement is based on how successful one is in continually recycling through the grant to research, to paper, to grant circle. Whoever coined that phrase is unknown to us, but the realities of academic success were clear, and we knew what we had to do. Science unpublished was not valued; the value of publication was academic success in terms of funding and position.

The late, great scientist, teacher and Nobel laureate Salvadore Luria, whose course in microbiology at MIT I attended and who some 20 years later I lived next door to in Lexington, Massachusetts, wrote in 1976 that "for the enthusiastic scientist, the scientific enterprise is a monument to humanity's power and freedom – a modern equivalent of the great cathedrals that the burghers of the middle ages raised as monuments to their newly found sense of economic power and freedom."[1] He went on to say that "[i]t is a fact of life that science has become so expensive that its support can be justified only on the basis of the benefits that derive from it, which is to say that science has to be justified by the practical technologies that it generates." His concern was that science will be diverted from its more pure purpose of knowledge-generation through objective methods and hypothesis-testing, to an involvement in "many of the questionable activities of society – a participation that in the long run is bound to undermine the rational heritage of science."

On this basis, and for several decades, the best of scientists and the best of their science lived in a bubble, in which application was outside the bubble and something that industry did, and that it was the job of business people to take scientific papers to products, while scientists simply plowed on, generating new grants, knowledge, and papers. And then something happened that changed the future course of science, imperceptibly at first, and now increasingly evident. That change was the passage of laws by the U.S. Congress ceding ownership of intellectual property to universities and scientists in government laboratories for discovery and inventions funded by federal research support. It has led us today to a new paradigm in science; picking up from the old paradigm, rephrased as knowledge generation and dissemination, we now must add knowledge translation, application, and finally evaluation. Instead of saying, as in the past, "if it's not read, it's not done," now we can say "if it's not used it's not done."

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1 S.E. Luria, *The Goals of Science*, profiles.nlm.nih.gov/QL/B/B/H/J/_/qlbbhj.pdf.

III. LEGISLATIVE INTERVENTION

In 1980, the Stevenson-Wydler Technology Innovation Act and the Bayh-Dole Act (officially Amendments to the Patent and Trademark Act) were signed into law, with the purpose of stimulating greater use of technologies developed through government support for research for scientists in government or academic laboratories. The background to this action was the concern expressed by Congress that federally-funded research led to patents held by the granting government agency, and that the sluggish government bureaucracy failed to move these discoveries forward to benefit the public. In fact, according to the U.S. General Accounting Office, only 5% of the more than 28,000 patents retained by the U.S. government had been licensed for use at that time, whereas 1/4 to 1/3 of patents held by industry were being applied. The reasons Congress became involved were several, some more lofty than others. For example, without application of discovery research supported by Federal funds, there was little in the way of return on the investment to the taxpayers who paid the bills, and the benefits of the research would be too long delayed or never realized. The more pedestrian concern was one of keeping U.S. industry competitive in the commercial world. The question was why there was so little action on government supported research and the answer seemed to be that government created too many barriers and too little incentive for either academia (not known for entrepreneurship) or the private sector (not known for openness about its product development pathways) to develop technology from the patents produced with government research support. A major barrier for industry was the fact that the government agencies "owning" the patents were reluctant to grant an exclusive license for companies that wanted this device to protect future earnings as the quid pro quo to invest their own money to develop the discovery into a product. While government appeared to be acting to protect the public's interest in the invention, its inaction, or perhaps misdirected action, was actually counter to the public's interest.

These two pieces of legislation, one covering academic research laboratories, and one covering government research laboratories (such as the National Institutes of Health), created a new climate in which academic institutions and government laboratories became much more interested in patenting and licensing the application of federally-supported research. These institutions clearly saw the potential of collecting licensing royalties on discoveries and inventions their faculty were already geared up to make. It was successful by any measure employed to assess the outcomes. One obvious consequence of the legislation was the initial slow, and then increasingly steep, rise in the number of universities setting up technology transfer and licensing offices. By 2006, however, the Annual U.S. Licensing Activity Survey of the Association of University Technology Managers (AUTM) reported the following amazing achievements:

- $45 billion in R&D support was received by U.S. academic centers, 2/3 from the government, and just 9% from industry
- 12,672 licenses and options were managed, yielding active income
- 697 new products originating from university research were introduced into the market in 2006, with 4,350 reported from just 1998 through 2006

- 553 new startup companies emerging from academia were launched in 2006
- 5,724 new spinouts were developed over the period from 1980 through 2006

IV. RESEARCHER PERSPECTIVES

Researchers are, by nature, entrepreneurial, albeit not necessarily in a commercial sense. To succeed in the competitive world of academic research requires not only intellectual and technical expertise, but also a willingness to "sell" one's work to the funding agencies and to one's peers. But this entrepreneurship does not necessarily or naturally extend to "selling" a product beyond the research outputs themselves. There were, and always will be, exceptions. For example, Genentech was co-founded in 1976 by Herbert Boyer of the University of California-San Francisco, who was a bit ahead of others in the academic world. Meanwhile, on the other coast, Biogen opened up a few years later, counting among its co-founders Walter Gilbert of Harvard and Phillip Sharp of MIT, both of whom subsequently were awarded the Nobel Prizes for their work. But the numbers of such scientist-entrepreneurs are relatively small. In a recent study, based on the database of a venture capital company, just 903 (8.6%) of 10,500 venture-backed founders of start-up firms in the database had an academic affiliation, with almost 2/3 holding positions in the professorial track.[2] Almost 16% more were researchers in university-based labs, but not in tenure-track positions. Of the 669 whose academic field was known, 45% came from engineering, and another 44% from medical or biological science or chemistry. However, more than 40% of those founding biotechnology companies were academics. In this field for sure, the movement of people from academia to the private sector has constituted an important mechanism for the translation of early stage upstream research, characteristic of university-based science, to product development and commercialization. These individuals for the most part came from top research universities, with Stanford and MIT topping the list, and the companies they founded tended to be in the same state as their institution, often close by.

For the rest of academic scientists, the focus has typically been on the research itself, and product development and commercialization has not been particularly visible on their radar screens. I offer my own experience as an example. My laboratory worked on the mechanisms of interaction of the bacterial protein, Shiga toxin, with human cells and its role in pathogenesis, with a long term goal of developing drugs or vaccines to prevent the illness we believed it played a major role in. Yet those goals were more appropriately classified as dreams, and did not preoccupy the work of the laboratory, which was focused on the basic studies of pathogenesis. In the course of the work, we developed a monoclonal antibody that recognized the several members of this toxin family, which we used to monitor protein purification. At the urging of the university technology transfer officer, who regularly mined

[2] Junfu Zhang, *A Study of Academic Entrepreneurs Using Venture Capital Data*, Institute for the Study of Labor (Bonn, Germany 2007), *available at* ideas.repec.org/p/iza/iza dps/dp2992.html.

grants issued and research progress, we allowed a patent application to go forward for the use of the antibody for diagnosis, treatment or prevention of illness, and this was issued in the mid-1990's. A diagnostic company contacted the university, and a licensing agreement was constructed that provided our antibody, which was formulated into a diagnostic test kit and then marketed. Although the kit would be useful for the infection of most interest to us, *Shigella dysenteriae* 1 in developing countries, the marketing and pricing was oriented towards the diagnosis of Shiga toxin producing *E. coli* causing bloody diarrhea and renal failure in the U.S., Europe and Japan. We had no clue that licensing could be structured in a manner that would have allowed us to influence the licensee to produce low-cost kits for developing countries experiencing epidemics of *S. dysenteriae* in Africa and South Asia. The "deal" was crafted by the office of technology transfer, and we were passive recipients of our portion of the royalties on sales that flowed from the arrangement.

The operative principle here is "no clue" because we were not previously exposed to the notion that a research laboratory could influence the way a license was structured, or indeed that we had anything of value since the "high value" patents being moved to the commercial sector were the extraordinary breakthrough science of the Boyer, Gilbert and Sharp type. Unfortunately for me, the new paradigm of discovery to product and impact on health, was not yet widely known - and in fact, not widely known by either researchers or by university technology managers. University presidents and academic leadership, especially at the handful of institutions making substantial amounts of royalty income, were not as concerned about the way the golden egg was being used than in the gold itself being returned to the institution. And so there was a status quo for the vast majority of university-based research - focus on research, grants and publication, and leave the issue of commercialization (whether, when, how, and for whom and for how much) to the tech transfer office. When we came to the fork in the road, science business-as-usual on one fork and product development and commercialization on the other, most of us took the first road because it was the route we knew.

V. IMPLEMENTING THE NEW PARADIGM

To be implemented, a new paradigm must be known and appreciated. Since we did not know where we were going, as the old adage states, any road would do, and we were drawn especially to the one we had already traveled. The past decade has been especially productive in convincing more and more scientists to take both roads - to continue to do their fundamental science, and to work on product development as well. In fact, there are a number of ways the latter can be pursued short of leaving academia and moving one's operation to the private sector. Some options rest in the choice of leads to follow and experiments to conduct. One way is in the deliberate development of collaborations with others with a greater applied research bent. Another option could actually be in the epidemiology that would underlie the fundamental decision to take a product forward for commercialization, because its meets an unmet need for which there is a potential market of users, and not in the development of the product itself.

What are the forces that have convinced more and more scientists in the health field to remove those old publish or perish blinders? Without any attempt to be encyclopedic, there are at least three that can be identified as having some real traction: funding, academic recognition, and social value.

A. Funding

The biggest impact has been made by the Bill and Melinda Gates Foundation, which began operations in 1999. Since then, its increasing endowment has been significantly turned towards addressing global disparities in health through a number of programs to develop new drugs and vaccines for neglected diseases, and to promote the basic research that underlies the ability to develop and deliver these products. At the same time the Foundation has invested in new public-private partnerships (PPPs) for drug and vaccine development, and increasingly in accelerating the access for vulnerable populations in developing countries to these products.[3] Only the Gates Foundation could invest almost $450 million dollars to create the Grand Challenges in Global Health program, funding research teams to overcome major barriers to advancement in 14 fields of interest.[4] And only Gates could commit $100 million over 5 years to its new program, Grand Challenges Explorations, to identify and fund very early stage innovative projects that could turn into a Grand Challenge project.[5] These Explorations require no preliminary data and impose no major administrative burden, hoping only for a return on the investment of at least one major advance and accept that nearly all will fail. The Gates Foundation has also invested in the other side of the coin, making products available to those in need with a vaccine purchase fund to permit developing countries to obtain the products to move through the enhanced delivery capacity of their health systems or by partnerships with academic institutions and/or non-governmental organizations.

However, Gates is only the latest, albeit now the biggest, foundation working in global health. The Rockefeller Foundation has a long tradition of investment in research and action to address health disparities dating from its establishment in 1913, when it focused on eliminating hookworm infection in poor rural populations in the southern United States. More recently, the Foundation has taken an early and major leadership role in the development of drug development PPPs, such as the International AIDS Vaccine Initiative, launched in 1996,[6] and the Global Alliance for Tuberculosis Drug Development, established in 2000.[7] Both organizations have made significant contributions in difficult R&D areas, and a pipeline of products and multiple

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[3] Global Health Program, Bill & Melinda Gates Foundation, www.gatesfoundation.org /GlobalHealth

[4] Harold Varmus, et al., *Grand challenges In Global Health*, 302 Science 398 (2003).

[5] Bill and Melinda Gates Foundation, Press Release, *New Initiative to Spur Innovation in Global Health Research*, www.gcgh.org/NewsEvents/MediaCenter.

[6] International AIDS Vaccine Initiative, www.iavi.org.

[7] Global Alliance for Tuberculosis Drug Development www.tballiance.org/home/home .php

sources of support, including funding from the Gates Foundation. It should be recognized, however, that the vision and the startup resources came from the Rockefeller Foundation. Another initiative of the Rockefeller Foundation is the Centre for the Management of Intellectual Property in Health Research and Development (MIHR), established in 2003 to promote best practices in the management of IP in developing countries.[8] Although funding constraints have forced MIHR into a period of quiescence (a testimony to the under-recognition by funders and donors of the potential role of developing and middle-income countries to contribute to new IP and product development to improve health) in the hope of restructuring and reemerging, among the many lasting contributions of this organization is the recently published tome, *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices*, published in 2007 and widely distributed in the developing world without cost, supported by sponsors and sales in developed countries.[9] MIHR and its partner, PIPRA, a similar organization focused on agricultural IP, has also issued an Executive Guide, with information specifically and separately directed towards policy makers, senior administrators, tech transfer managers, and of particular relevance to this discussion, for scientific researchers as well.

B. Recognition

Academics sometimes lead innovation in education; sometimes they follow leads. In the case of insuring that intellectual property is used to promote development of and access to products to address global health disparities, students have played a major role in pushing universities to take action and to promote better translation of research to products, with considerable attention to the needs of the underserved in developing countries. A good example of student push comes from Yale University, where students at the law school pressured the administration to, in turn, pressure Bristol-Myers-Squibb.[10] Bristol-Myers manufactures the drug d4T on a license from Yale, the patent holder. Students organized to make the drug available at affordable prices in developing countries. Partly in response to specific issues, such as this, and in part as a response to increasing interest in global health among students, a number of institutions are developing initiatives, centers, or institutes for global health to capture the excitement and coordinate the education, research, and outreach efforts of the university. Some of this interest has been fueled by the involvement of celebrity activists who capture media attention and help to raise both awareness and money. The rise of social entrepreneurship — the use of entrepreneurial principles to address and alleviate a social problem — is increasingly driving students at schools of business or management to consider how they can reconcile a career in the for-profit sector with philanthropy and/or meaningful changes in corporate practice that both generate profit and create access to technology

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[8] Centre for the Management of Intellectual Property in Health Research (MIHR), www.mihr.org

[9] IP Handbook of Best Practices, www.iphandbook.org/handbook.

[10] Amy Kapczynski, *Yale's Patent Policy Unfit for AIDS Medicines*, Yale Daily News, Oct. 19, 2001, *available at* www.yaledailynews.com/articles/view/1965.

at affordable prices in poor nations. Schools are responding with new courses and programs, and foundations and other private sector organizations are getting on board as well.[11]

What makes it possible for faculty to fully participate in the R&D part of this new movement among academics and students is when universities begin to seriously recognize the importance of research and scholarship in this field and recognize by appointments and promotion not only those who do the fundamental research, but also those who do the translational research, and applied and evaluation research in the community. This too is promoted in the U.S. by the National Institutes of Health's Roadmap initiatives in translational research and the global health research, and capacity strengthening programs of NIH's Fogarty International Center. Of course, the funding provided by Foundations, such as Gates, is attracting increased participation by universities, even though Foundations do not provide for the same level of indirect costs for research that Federal funding gives, and which the universities depend upon. In a retrogressive move, a few institutions among the research-intensive universities are actively discouraging faculty from applying for Foundation funding, because of their concern for the costs to the institution, and because they prefer Federal indirect cost rates to that of the Foundations. If current trends continue, however, it is hard to see how universities will sustain such policies.

From the technology transfer side of the equation, the Association of University Technology Managers has given increased attention to the need for creative licensing practices. In 2003, an interest group in global health issues was created at AUTM, Technology Managers for Global Health, which meets with interested membership and organizes symposia at the annual AUTM meetings and at other relevant conferences. This has helped to create a greater momentum among technology transfer managers to develop the necessary perspective on health disparities and the importance of ensuring that IP does not restrict access to technology in developing countries. The result is a greater partnership between researchers and technology transfer officers, each of which has been sensitized by the many initiatives surrounding them, to which they find it increasingly difficult to shut out by focusing on their primary role. As constituency awareness and university recognition of their efforts to bridge the gaps converge, more of this will happen.

C. Social value

Some of the growing concern for health disparities has been noted above. However, when USA Today reports on the growing social consciousness among the kids of Generation Y,[12] you have to believe something is happening. Citing various recent surveys of attitudes and concerns of this group of young people, now in high school or college or just entering the work force, over 60% of the 13-25 year old age group feel personally responsible for making a difference in the world through their work and actions, and 2/3 believe that it

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[11] Social Entrepreneurship Links, www.xpdnc.com/links/sntrprnr.html; Social Venture Network, www.svn.org; Bioventures for Global Health, www.bvgh.org.

[12] Sharon Jayson, *Generation Y Gets Involved*, USA Today, Oct. 23, 2006, *available at* www.usatoday.com/news/nation/2006-10-23-gen-next-cover_x.htm.

is important to help others who experience difficulties in life. As a consequence, volunteerism and community service is rapidly increasing among college students, focused both locally and globally. The issues of greatest importance to them after education are poverty, environment, health and disease, drug and alcohol prevention, human rights and political freedom, and equal rights, followed by disaster relief, AIDS, and hunger. The exceptional use of the internet by this generation has promoted both social concern as well as social networking, and in part these two overlap. Gen Y kids are more apt today to sign and email a petition for social action, physically protest, or actively contact a government official over their social concerns. Finally the article reported that 79% of those already employed stated that they "want to work for a company that cares about how it affects or contributes to society." These are very hopeful signs, compared to the "me-generation" of baby-boomers during the 1990s.

SUMMARY AND CONCLUSIONS

There is a simple underlying message in this discussion, which has three parts. First, science has the capacity to generate new knowledge and harness that knowledge in the cause of developing products and technology that can reduce disease burdens among developing nation populations. Second, intellectual property is a tool to use in order to insure that new knowledge is not expropriated and exploited in a manner that threatens the ability to provide products and technology to poor people at an affordable price. Third, and finally, academic scientists need to understand that they can stride both pathways of the R&D road, remaining involved in generating basic knowledge while participating in the application of that knowledge towards product development and, through the use of best practice IP management, making it available in resource-poor environments.

In order for this to happen, academia needs to maintain bridges to the private sector, while assiduously avoiding financial conflicts of interest, a topic not discussed in this paper. Academic scientists, whether already established or still completing their education, need access to training modules that allows them to define the challenges of the high disease burdens in the third world in human, and not just in consumption or dollar, terms. They also need education regarding the problems they work on, in order to engage them in the technology transfer from academia to the private sector; promote collaboration with scientists in the developing world; provide them with enough insights into the process and how it operates so that they know about the terms of any agreements with the private sector that would prevent poor people from accessing the ultimate product; and finally "reward" them in the academic system by advancement based on applied and field-based international translational and operational applied research. If these education programs develop and expand to increasing numbers of people in the research sector of academia, the number of people taking both paths described here will substantially increase. With that, the amount of research relevant to improving the health status - and indirectly, development - of developing countries will have been substantially increased.